Radiology

High-Intensity Focused Ultrasound for Treatment of Symptomatic Benign Thyroid Nodules: A Prospective Study[1]

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Purpose: To evaluate first-year efficacy and changes in pressure symptoms and health-related quality of life (HRQOL) after ultrasonographically (US) guided high-intensity focused ultrasound (HIFU) ablation of symptomatic benign thyroid nodules.

Materials and Methods: After ethics approval and informed consent were obtained, a prospective trial was conducted. Patients with a symptomatic benign thyroid nodule were given a choice of HIFU treatment or active surveillance. Clinical and US examinations, pressure symptom scores (visual analog scale), and HRQOL questionnaires (short form-12 survey) were evaluated at baseline and at 3, 6, and 12 months. The primary outcome was change in nodule volume after 12 months. The percentage of change in nodule volume was defined as the baseline volume minus the volume at 12 months divided by the baseline volume times 100. Ablation success was defined as a reduction in volume of greater than 50%. Nodule volume was compared by using the paired *t* test. Continuous variables were compared by using the Mann-Whitney *U* test, and categorical variables were compared by using χ^2 tests.

Results: Twenty-two patients underwent HIFU and 22 underwent active surveillance. Mean age was 53.11 years (range, 28–76 years) and 55.19 years (range, 41–70 years), respectively. The ratio of men to women was 2:20 and 1:21, respectively. The 12-month mean volume reduction ± standard deviation in the HIFU group was significant (68.87% ± 15.27 [range, 47.35%–94.89%], $P < .001$) but not in the surveillance group (−2.11% ± 6.29 [range, −15.64% to 12.70%], $P > .05$). Preablation nodule volume was the only determinant of ablation success (odds ratio, 1.877; 95% confidence interval [CI]: 1.085, 3.249; $P = .024$). At 12 months, patients in the HIFU group had less swelling ($P < .001$), lower pressure symptom scores ($P < .001$), and higher physical composite scores ($P = .006$). Physical composite scores significantly correlated with 6-month reduction in nodule size ($r = 0.768$; 95% CI: 0.660, 0.930; $P < .001$) and 12-month reduction in nodule size ($r = 0.704$; 95% CI: 0.680, 940; $P < .001$).

Conclusion: HIFU ablation of symptomatic benign thyroid nodules not only induced significant shrinkage but also improved pressure symptom scores and HRQOL throughout a 12-month period.

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Thyroid nodules are common and could be discovered with clinical palpation in 5% of healthy individuals and with high-resolution ultrasonography (US) in 60% of the general population (1,2). However, since most nodules are benign and do not grow rapidly, surgical resection is only indicated when they become large (>4 cm) or are causing obstructive and/or local pressure symptoms (1–5). Surgical resection has remained the mainstay of treatment for symptomatic benign thyroid nodules and is considered safe when it is performed by an experienced surgeon. Nevertheless, there is a risk of complications, and surgery is associated with high cost and the need for general anesthesia. As a result, there has been a growing interest in developing nonsurgical, minimally invasive techniques for the treatment of symptomatic benign thyroid nodules (6,7). These minimally invasive techniques include percutaneous ethanol injection therapy, laser ablation therapy, and radiofrequency ablation (8–10). Percutaneous ethanol injection therapy is effective in thyroid cysts and is recommended for recurrent, benign thyroid cysts (1,8). However, for solid or predominantly solid nodules, thermal ablation techniques such as laser ablation therapy and radiofrequency ablation are generally more effective (9–11). Authors of studies (10,11) have found that these techniques could not only result in greater than 50% reduction in nodule size but also relieve pressure symptoms in many patients.

High-intensity focused ultrasound (HIFU) is another emerging thermal ablation technique, but, to our knowledge, it is less well described in the literature. Its major advantage over other thermal techniques is that it could induce a focused thermal destruction of tissue with temperatures of up to 85°C without needle puncture and skin penetration (6). Results of studies (12,13) have shown HIFU ablation could cause moderate nodule shrinkage within the first few months. However, to date, HIFU only has been applied in relatively small nodules and in patients with less well-defined nodule-related symptoms (12–14). Therefore, it remains unclear how effective HIFU ablation is at relieving obstructive or pressure symptoms and, more importantly, at improving well-being or health-related quality of life (HRQOL) of patients relative to those who do not undergo ablation. Given these issues, a prospective study was conducted to evaluate the treatment efficacy (ie, extent of nodule shrinkage at 12 months) and changes in symptom severity and HRQOL after a single session of HIFU ablation.

Advances in Knowledge

- Our data showed that the application of high-intensity focused ultrasound (HIFU) ablation to benign thyroid nodules not only induced significant 12-month nodule shrinkage from baseline (median, 76.04%; interquartile range [IQR], 47.54%; $P < .001$) but also improved pressure symptom scores (baseline median score, 5.0; IQR, 2.3; 6-month median score, 3.0; IQR, 1.5% [$P < .001$]; and 12-month median score, 1.0; IQR, 1.0 [$P < .001$]).
- The difference in median physical composite scores for health-related quality of life between baseline and 12 months was significantly different between the HIFU and control groups (5 vs −1, respectively; $P = .006$).
- Initial (preablation) nodule volume (odds ratio, 1.877; 95% confidence interval [CI]: 1.085, .249; $P = .024$) was the only determinant of 12-month ablation success (> 50% volume reduction from baseline).

Implication for Patient Care

- For patients with benign thyroid nodules who are candidates for surgical resection but are reluctant to undergo thyroidectomy, HIFU ablation might be a better therapeutic option than active surveillance alone because of the significant shrinkage in nodule size, reduced pressure symptoms, and improved health-related quality of life in the 12 months after ablation.

Materials and Methods

The device for the US-guided HIFU treatment was owned by our institution, and there was no financial support given from the industry. The authors had complete control of the data and the information for publications. This prospective trial was approved by the local institutional review board (UW15–486) and was registered at *www.clinicalTrials.gov* (NCT02658552) before patients were recruited. From July to October 2015, consecutive patients who presented for the first time with a thyroid swelling were evaluated. First, to be eligible, the swelling was required to be benign (ie, Bethesda class II at cytologic evaluation of a fine needle aspiration specimen [15] within 3 months and sonographic pattern on US images with low or very low suspicion of malignancy) (2). Second, the swelling (which could be either a solitary nodule or a dominant nodule in a multinodular gland) was required to be causing obstructive or pressure symptoms. Patients with swelling that was causing only nonspecific neck complaints or cosmetic concerns were not included. Third, the index

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Abbreviations:
CI = confidence interval
HIFU = high-intensity focused ultrasound
HRQOL = health-related quality of life
IQR = interquartile range
VAS = visual analog scale
WHO = World Health Organization

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Guarantor of integrity of entire study, B.H.H.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, B.H.H.L., Y.C.W.; clinical studies, B.H.H.L.; statistical analysis, B.H.H.L., C.K.H.W.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

nodule was required to be larger than or equal to 10 mm but smaller than or equal to 40 mm on US images in three orthogonal dimensions. Fourth, given the association between thermal ablation efficacy and the proportion of solidity in the nodule (6,7), the index nodule was required to be at least 70% solid on US images. This requirement was determined by a dedicated clinician who was not directly involved with our study. Fifth, the index nodule was required to be within the treatable depth for ablation (ie, 5–30 mm between skin and the nodule center). Sixth, patients were required to have serum levels of free thyroxine, thyrotropin, and calcitonin within the reference range. Last, patients were required to have decided not to undergo surgical resection as treatment. The study exclusion criteria were age of 18 years old or younger; current pregnancy or lactation; index nodule with indeterminate or malignant findings at cytologic evaluation of fine needle aspiration specimen, thyrotropin level outside the reference range, or intranodular macrocalcifications (ie, precluding HIFU treatment); history of head and neck irradiation; family history of nonmedullary thyroid carcinoma; preexisting vocal cord palsy; or any medical conditions precluding intravenous sedation.

Patients who met these criteria were asked to participate. Each patient was counseled about HIFU treatment and the alternative (ie, active surveillance) and then was asked to choose. Those who preferred HIFU received one session of ablation in the outpatient setting (HIFU group), while no active treatment was given to those who chose active surveillance (surveillance group). In both groups, the index nodule was closely monitored with US throughout a 12-month period.

Pretreatment Evaluation

All swellings were clinically graded according to the World Health Organization (WHO) grading system (16) by a dedicated clinician who was not directly involved with our study. Pressure symptoms were evaluated on a visual analog scale (VAS of 0–10). Nodule dimensions were measured with US by using a system (LOGIQ *e*; GE Healthcare, Milwaukee, Wis) equipped with a 10–14-MHz linear matrix transducer. An independent experienced sonographer who was not aware of the patients' treatment choice made all measurements. Three orthogonal diameters of the index nodule (its longest diameter and two other perpendicular diameters) were measured. In general, the longest diameter was the craniocaudal dimension (length) of the nodule, while the other two perpendicular diameters were the mediolateral (width) and anteroposterior (depth) dimensions of the nodule. All nodules were measured to the nearest 0.1 mm. To estimate nodule volume, we used the formula: $V = (W \cdot D \cdot L) \cdot (\pi/6)$, where V is volume in milliliters; W is width, D is depth, and L is length in centimeters; and π is 3.1416. In addition to dimensions, the number of other nodules larger than 1 cm and the side and location of the nodule in the lobe (ie, upper, middle, or lower thirds) were recorded. Patients' body weight (in kilograms), height (in centimeters), serum thyrotropin (in milli-international units per liter), and free thyroxine (in picomoles per liter) were also checked. In addition, patients in both groups were asked to fill out an HRQOL (SF-12) questionnaire.

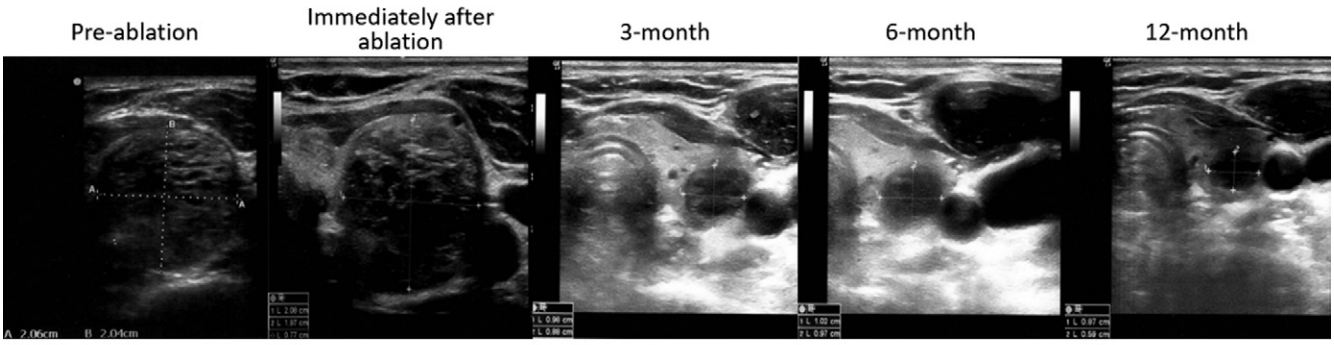
HIFU Ablation

All treatments were performed by one surgeon (B.H.L., with 14 months of experience) with a US-guided HIFU system (EchoPulse; Theraclion, Paris, France). This system comprised an energy generator, a treatment head, a skin-cooling device, and a touch-screen interface for planning (Fig 1a). The treatment head incorporated an imaging transducer (7.5 MHz, 128 elements, linear array) and an HIFU transducer (3 MHz, single element, 60 mm in diameter). After they were positioned, patients were sedated with diazepam (10–15 mg) and pethidine (50–100 mg). Under US guidance, the treatment head was adjusted until the entire index nodule was within the treatable depth. The HIFU computer (Beamotion version TUS 3.2.2; Theraclion) automatically divided the nodule into multiple ablation subunits. Each subunit was approximately 7.3 mm thick and 5 mm wide. Each subunit received continuous 8-second pulses of HIFU energy followed by 40 seconds of cooling time before the beam moved to the adjacent subunit. This cycle continued until all subunits were ablated. To ensure safety, nearby structures such as the carotid artery, trachea, and skin were marked on the treatment screen and left unablated. At any point during the treatments, the operators were able to omit subunits if they were deemed too close to vital structures. A laser-based movement detector enabled immediate power interruption when the patient moved or swallowed during ablation. To avoid burning the skin, a balloon filled with liquids at 10°C was used to cool the skin at the tip of the treatment head. All ablations started at 204 Sv per pulse and increased up to 280 Sv per pulse until a hyperechoic mark appeared (Fig 1a). Total treatment time included the time taken for treatment head positioning, planning, and energy delivery. During treatment, patients' vital signs were continuously monitored. Skin burns, soft-tissue swelling, and hoarseness of voice during HIFU were recorded. Patients were asked to rate their pain during treatment, immediately after treatment, and before discharge on a VAS (0 = no pain and 10 = worse possible pain). Afterward, transcutaneous laryngeal US was performed to assess the mobility of both vocal cords (17).

Follow-up Evaluation

In the first week, any specific problems or concerns were recorded. In the HIFU group, the treated nodule was measured with US at 1 week and 1, 3, 6, and 12 months. In the surveillance group, the nodule was measured with US at 3, 6, and 12 months. The percentage of change in volume was calculated with the following equation: $(V_{baseline} - V_{visit})/(V_{baseline}) \cdot 100$, where $V_{baseline}$ is volume at baseline and V_{visit} is volume at the visit. The primary outcome was a change in volume (in milliliters) of the index (or treated) thyroid nodule 12 months after a single session of HIFU. Ablation success was defined as greater than 50% reduction in volume from that at baseline. At 6 and 12 months, nodules of patients in both groups were assessed clinically by using the WHO grading system (16), and patients were asked to rate their

Figure 1



b.

a.

Figure 1: **(a)** Touch-screen interface of HIFU machine. Central panel shows top view reconstruction of nodule, which is made of multiple white circles. Empty circles represent unablated subunits and filled circles represent ablated subunits. Image *A* is the planned image, and image *B* is the actual real-time image during treatment. Hyperechoic marks (a sign of tissue necrosis) are indicated with two black arrows on image *B*. **(b)** US images were obtained before treatment, immediately after, and at 3, 6, and 12 months after treatment.

pressure symptoms by using the VAS and to rate the improvement in their obstructive and/or local pressure symptoms since baseline (0 = same, 1 = slight improvement, 2 = moderate improvement, 3 = substantial improvement). HRQOL (short form-12) questionnaires also were evaluated at 3, 6, and 12 months.

Statistical Analysis

Continuous variables were expressed as means ± standard deviation and as medians and interquartile range (IQR) when appropriate. The IQR was defined as the distance between the third and first quartile. Groups were compared by using the Mann-Whitney *U* test. χ^2 tests were used to compare categorical variables. For correlation between continuous variables, Spearman rho correlation tests were performed. For the description and interpretation of correlation estimates, 0–0.19 was regarded as very weak strength of correlation, 0.2–0.39 as weak, 0.40–0.59 as moderate, 0.6–0.79 as strong, and 0.8–1 as very strong. Both the univariate and multivariate analyses were performed by using logistic regression analysis. Any parameters that were significantly associated with ablation success in the univariate analysis were entered into multivariate analysis. Pressure symptoms were rated on a VAS of 0–10 at baseline and at 6 and 12 months after treatment. Changes in VAS and HRQOL scores between groups over time and their interactions were evaluated by using the Wilcoxon signed-rank test.

All statistical analyses were conducted by using software (SPSS version 18.0, SPSS, Chicago, Ill; and R version 2.14.0, R Foundation for Statistical Computing, Vienna, Austria). *P* values less than or equal to .05 were considered to indicate a significant difference.

Results

Of the 52 eligible patients, 44 (84.6%) agreed to participate in our study. Twenty-two patients agreed to undergo HIFU ablation, while another 22 patients preferred active surveillance. For patients with multiple nodules, only the largest (or dominant) nodule was ablated. All HIFU group patients underwent HIFU ablation without interruption and were discharged on the same day. All patients completed their scheduled visits and no one was lost to follow-up.

There were no significant differences in baseline demographics, weight, height, body mass index, serum thyrotropin and free thyroxine levels, and clinical nodule size (according to the WHO grading system) between the two groups (Table 1). However, on US images, the nodules were significantly longer in the HIFU group (3.14 cm vs 2.38 cm, $P = .019$) and nodule volume was also significantly greater (6.98 mL vs 4.09 mL, $P = .015$). Other parameters such as width ($P = .133$) and depth ($P = .828$) of the nodule, proportion of solidity ($P = .747$), distance between skin and nodule center ($P = .920$), nodule side ($P = .827$) and location ($P = .519$), and mean number of other nodules larger than 1 cm ($P = .384$) were comparable.

Treatment parameters are shown in Table 2. Pain was most severe during ablation (median, 3.5; IQR, 4.0) but improved immediately after ablation (median, 1.0; IQR, 1.0). During ablation, six (27.3%) patients had pain radiating to the ipsilateral shoulders and arms, while the rest had pain at the site of ablation only. At discharge, the pain score fell to almost zero (median, 0; IQR, 1.0). Only three (13.6%) patients had mild residual discomfort at the week 1 visit. No patients had skin burns or hoarseness. Skin redness and minor swelling were noted in 10 (45.5%) patients, but they all improved in the first week. On transcutaneous laryngeal US images, all had mobile bilateral vocal cords after ablation.

Table 1

Baseline Patient Characteristics and Preoperative US Findings

Characteristic or Finding	HIFU Group ($n = 22$)	Surveillance Group ($n = 22$)	*P* Value
Age at treatment (y)*	53.11 ± 11.40	55.19 ± 8.2	.606†
Sex	2/20	1/21	>.999‡
Male	2	1	
Female	20	21	
Body weight (kg)*	60.11 ± 11.74	58.31 ± 10.40	.856†
Height (cm)*	159.87 ± 7.42	157.87 ± 4.27	.238†
Body mass index (kg/m^2)*	23.36 ± 3.27	24.00 ± 3.51	.521†
Thyrotropin (mIU/L)*	1.25 ± 1.53	1.27 ± 1.30	.087†
Free thyroxine (pmol/L)*	16.07 ± 2.91	17.42 ± 1.46	.256†
Previous thyroid surgery	4 (18.2)	1 (4.5)	.162‡
WHO nodule grade at presentation			.723‡
Grade 1a (palpable but not visible when neck is extended)	0 (0.0)	0 (0.0)	
Grade 1b (palpable and visible when neck extended)	4 (18.2)	5 (22.7)	
Grade 2 (visible when neck is in the normal position)	12 (54.5)	14 (63.6)	
Grade 3 (visible from distance)	6 (27.3)	3 (13.6)	
Index nodule at US			
Dimension and size*			
Width (cm)	2.26 ± 0.54	1.99 ± 0.38	.133†
Length (cm)	3.14 ± 0.75	2.38 ± 0.92	.019†§
Depth (cm)	1.74 ± 0.42	1.68 ± 0.36	.828†
Volume (mL)#	6.98 ± 4.04	4.09 ± 1.99	.015†§
Distance from skin to center of nodule (mm)	19.73 ± 4.30	18.0 ± 7.34	.920†
Side			.827‡
Right	10	11	
Left	10	10	
Isthmus	2	1	
Location within the lobe			.519‡
Upper third	3	2	
Middle third	6	3	
Lower third	13	17	
Mean no. of other nodules at US*	1.95 ± 1.43	1.59 ± 1.37	.384†
Median‖	2 (1.3)	2 (2.0)	
0 nodules	4 (18.2)	6 (27.3)	.831‡
1 nodule	3 (13.6)	4 (18.2)	
2 nodules	10 (45.5)	8 (36.4)	
3–5 nodules	5 (22.7)	4 (18.2)	

Note.—Unless otherwise indicated, data in parentheses are percentages. Only nodules larger than 1 cm on US images were included.

* Data are means ± standard deviation.

† Mann-Whitney *U* test was used.

‡ χ^2 test was used.

§ Indicates a significant difference.

Equation for volume of nodule: $V = (W \cdot D \cdot L) \cdot (\pi/6)$, where V is volume, W is width, D is depth, L is length, and π is 3.1416.

‖ Data in parentheses are IQRs.

Table 2

Size Change of Dominant Nodule in HIFU and Active Surveillance Groups

Variable	HIFU Group (n = 22)	Surveillance Group (n = 22)	P Value
Treatment parameters			...
Estimated treated volume (mL)*	4.59 ± 1.78 (2.21–8.13)	...	
Total energy delivered (KSv)*	15.17 ± 6.90 (5.88–28.35)	...	
Energy per volume per mL (KSv)*	4.08 ± 0.81 (2.78–6.13)	...	
Total duration of treatment (min)*	75.71 ± 34.20 (48.75–153.25)	...	
Pain scores based on VAS*			...
During treatment	4.43 ± 2.14	...	
Immediately after treatment	1.43 ± 1.16	...	
Before hospital discharge	0.36 ± 0.50	...	
Volume of index nodule (mL)*			
Baseline	6.98 ± 4.04	4.09 ± 1.99	.019†
1 week	7.02 ± 4.15	...	
1 month	6.82 ± 3.45	...	
3 months	3.17 ± 3.28	4.12 ± 1.96	.183
6 months	3.02 ± 2.66	4.18 ± 2.03	.010†
12 months	2.81 ± 2.44	4.19 ± 2.04	.008†
Volume reduction (%)*			
1 week	−0.00 ± 4.66	...	
1 month	22.44 ± 11.84‡	...	
3 months	61.55 ± 16.68‡	−0.83 ± 6.85‡	<.001†
6 months	66.91 ± 16.27‡§	−1.99 ± 6.13‡	<.001†
12 months	68.87 ± 15.27‡#	−2.11 ± 6.29†	<.001†
WHO nodule grade at 12 months			<.001†
Grade 1a (palpable but not visible when neck is extended)	13 (59.1)	0 (0.0)	
Grade 1b (palpable and visible when neck extended)	6 (27.3)	5 (22.7)	
Grade 2 (visible when neck is in the normal position)	3 (13.6)	13 (59.1)	
Grade 3 (visible from distance)	0 (0.0)	4 (18.2)	
Symptom improvement score			<.001†
0 (no improvement)	0 (0.0)	8 (36.4)	
1 (slight improvement)	2 (9.1)	12 (54.5)	
2 (moderate improvement)	6 (27.3)	2 (9.1)	
3 (significant improvement)	14 (63.6)	0 (0.0)	

Note.—Unless otherwise indicated, data are number of patients, with percentages in parentheses.

* Data are means ± standard deviation, with the range in parentheses.

† Indicates a significant difference.

‡ $P < .05$ relative to baseline.

§ $P > .05$ between 3 months and 6 months.

$P > .05$ between 6 months and 12 months.

Volume Reduction after HIFU Ablation

The mean nodule volume did not change significantly at 1 week (6.98 mL ± 4.04 [median, 6.33 mL; IQR, 15.08 mL] vs 7.02 mL ± 4.15 [median, 3.44 mL; IQR, 7.83 mL]; P = .395) (Fig 1b). In fact, eight (36.4%) patients had a mean increase of 3.73% ± 2.37 (median, −3.25%; IQR, 7.10%) while the rest either had similar size (± 1%; n = 6) or reduced size (n = 8), with a mean of 5.46% ± 5.24 (median, 3.71%; IQR, 13.31%). At 1 month, all patients had a reduced volume, with a mean reduction of 22.58% ± 9.23 (median, 20.14%; IQR, 34.19%). At 3 months, all patients had a mean volume reduction of 61.54% ± 16.68 (median, 59.95%; IQR, 27.18%). Eighteen (81.8%) patients achieved ablation success at 3 months. At 6 months, all patients had a mean volume reduction of 66.91% ± 16.28 (median, 73.75%; IQR, 26.11%) (Fig 2) but similar to that at 3 months, 18 (81.8%) patients achieved ablation success. At 12 months, all patients had a mean volume reduction of 68.87% ± 15.27 (median, 76.04%; IQR, 25.44%) (Fig 2), but it was similar to that at 6 months, when 18 (81.8%) patients achieved ablation success. Although there was a significant volume reduction at 1 month and 3, 6, and 12 months from baseline ($P < .05$), there was no significant volume reduction between 3 months and 6 months (P = .096) or between 6 months and 12 months (P = .078) in the HIFU group. In the surveillance group, there was a nonsignificant size increase at 3 months (P = .699), 6 months (P = .159), and 12 months (P = .148) from that at baseline.

Correlation between Preablation Nodule Volume and Treatment Parameters

There was a significant correlation between preablation nodule volume and total energy delivered (r = 0.854; 95% confidence interval [CI]: 0.680, 0.940; $P < .001$) and also between preablation nodule volume and total treatment time (r = 0.989; 95% CI: 0.970, 1.000, $P < .001$). However, there was no correlation between preablation nodule volume and mean energy (in millisieverts) per milliliter (r = 0.115; 95% CI: −0.310, 0.520; P = .398).

Factors That Led to Ablation Success at 12 Months

At univariate analysis, smaller preablation nodule volume (odds ratio, 1.877; 95% CI: 1.085, 3.249; P = .024) was a significant factor leading to ablation success (Table 3).

Pressure Symptoms Rated on a VAS

According to the self-estimated rating on a VAS, mean pressure symptoms in the HIFU group were significantly reduced from 5.09 ± 1.66 (median, 5.0; IQR, 2.3) at baseline to 2.05 ± 1.29 (median, 3.0; IQR, 1.5) at 6

Figure 2

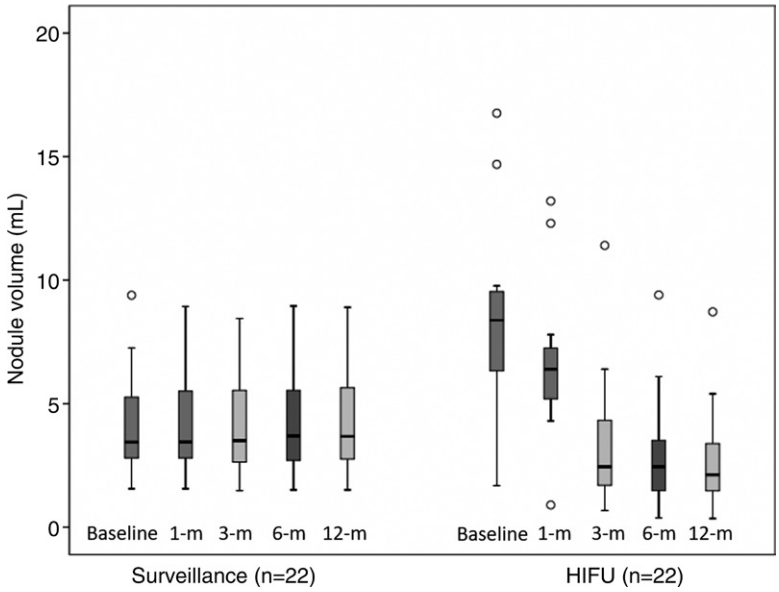


Figure 2: Boxplot shows mean volume of thyroid nodule for patients who underwent HIFU ablation and those who underwent surveillance (control subjects).

Table 3

Logistic Regression Analysis of Factors Predictive of Ablation Success

	Ablation Success Univariate Analysis	
Variable	Odds Ratio	*P* Value
Age	1.034 (0.905, 1.182)	.624
Sex	0.810 (0.628, 1.427)	>.999
Body mass index	1.310 (0.815, 2.107)	.265
Preablation nodule volume*	1.877 (1.085, 3.249)	.024†
Distance from skin to center of nodule	0.172 (0.024, 107.272)	.363
Side of nodule	1.105 (0.142, .597)	.924
Location of nodule	0.143 (0.004, 4.612)	.272
Estimated treated volume	1.040 (0.425, 2.544)	.931
Total energy delivered	1.033 (0.825, 1.109)	.715
Mean energy delivered per milliliter	1.023 (0.920, 1.080)	>.999
Total duration of treatment	1.043 (0.981, 1.109)	.178

Note.—Data in parentheses are 95% CIs. Ablation success at univariate analysis was defined as >50% reduction in volume at 12 months. Entered as a dichotomized variable (>50% or ≤50%); there were 18 (81.8%) patients who achieved ablation success.

* Equation for volume: $V = (W \cdot D \cdot L) \cdot (\pi/6)$, where V is volume; W is width, D is depth, and L was length; and π is 3.1416.

† Indicates a significant difference.

months ($P < .001$) and to 1.14 ± 1.13 (median, 1.0; IQR, 1.0) at 12 months ($P < .001$), while relative to baseline, pressure symptoms in the surveillance group remained the same at 6 months ($P = .754$) and at 12 months ($P = .088$) (Fig 3).

Clinical Nodule Grade and Symptom Improvement

In the surveillance group, the proportion of WHO nodule grades 1, 2, and 3 did not change in the 12-month period, whereas in the HIFU group, every patient had a lower WHO grade after HIFU ($P < .001$). Of the six patients with a WHO grade of 3, three (50%) patients were subsequently assessed as grade 2, and three were assessed as grade 1b. Similarly, nine patients with WHO grade 2 nodules were later assessed as grade 1a and three were assessed as grade 1b. Relative to the surveillance group, the HIFU group had significantly higher median and IQR symptom improvement scores (3.0 [IQR, 1] vs 1.0 [IQR, 1], $P < .001$).

HRQOL Assessment

For the physical composite scores, at 3 months versus baseline, 6 months versus baseline, and 12 months versus baseline, there were significant differences between the HIFU and surveillance groups (median score, 4 vs 0 [$P = .001$]; 2 vs 1, [$P = .025$]; 5 vs 1 [$P = .006$]; respectively) (Table 4). For role physical, at 3 months vs baseline, 6 months vs baseline, and 12 months vs baseline, there were significant differences between HIFU and surveillance groups (median, 0 vs 0 [$P = .011$]; 0 vs 0 [$P = .019$]; and 0 vs 0 [$P = .005$]; respectively). For bodily pain, at 6 months versus baseline and at 12 months versus baseline, there were significant differences between the HIFU and surveillance groups (median, 0 vs 0 [$P = .029$] and 0 vs 0 [$P = .008$], respectively). For general health, at 3 months versus baseline, 6 months versus baseline, and 12 months versus baseline, there were significant differences between the HIFU and surveillance groups (median, 35 vs 0 [$P = .003$]; 35 vs 0 [$P = .006$]; and 35 vs 0 [$P = .007$], respectively). For social functioning, at 6 months versus baseline and 12 months versus baseline, there were significant differences between the HIFU and surveillance groups (median, 0 vs 0 [$P = .006$] and 0 vs 25 [$P = .006$], respectively). For role emotional, at 12 months versus baseline, there was a significant difference between the HIFU and surveillance groups (median, 0 vs 0 [$P = .045$]).

Improvements in the physical composite scores from preablation to 12

Figure 3

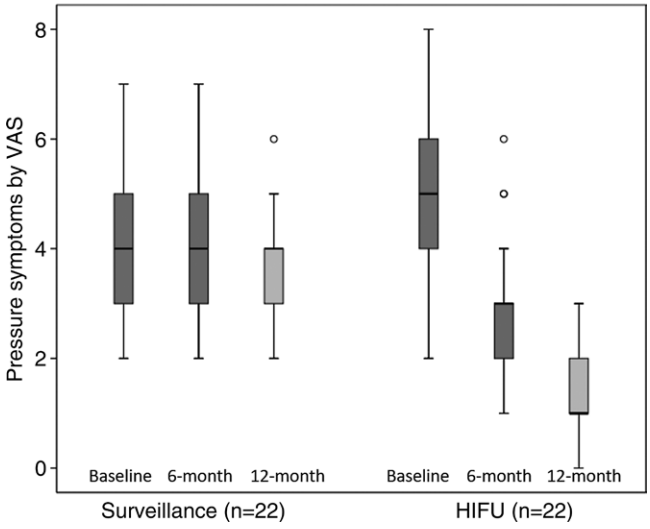


Figure 3: Boxplot shows pressure symptoms rated according to VAS of 0–10 at baseline, 6 months, and 12 months for HIFU and active surveillance (control subject) groups.

months were related to nodule size reduction at 6 months (r = 0.768; 95% CI: 0.660, 0.930; $P < .001$) and nodule size reduction at 12 months (r = 0.704; 95% CI: 0.680, 940; $P < .001$) but not related to age (r = −0.071; 95% CI: −0.420, 0.420; P = .570), body mass index (r = −0.011; 95% CI: −0.520, 0.310; P = −.925), preablation volume (r = −0.136; 95% CI: −0.520, 0.320; P = .272), preablation thyrotropin level (r = −0.025; 95% CI: −0.670, 0.090; P = .922), and free thyroxine level (r = −0.115; 95% CI: −0.680, 0.100; P = .398).

Discussion

Although most cytologically benign thyroid nodules do not require any intervention other than surveillance, some do become large and cause obstructive and/or local pressure symptoms (3–5). In that situation, surgery either in the form of lobectomy or total thyroidectomy is the most effective therapeutic option (1,2). However, although surgery is a recommended treatment (1,2), some patients do not wish to undergo surgery. Risk of surgical complications, high cost, need for general anesthesia, and permanent loss of thyroid parenchyma are, perhaps, some of the reasons for patient reluctance (6,7). As a consequence, there is considerable interest in identifying nonsurgical alternatives. Among them, HIFU is one of the most minimally invasive, because no needle puncture or skin penetration is required during treatment.

In addition to confirming that there was a significant volume reduction in benign thyroid nodules in the first 3–6 months after ablation as there was in previous studies (12–14), our study results showed (for the first time, to our knowledge) that there was a continuing volume reduction beyond 6 months after HIFU ablation. At 12 months, the overall mean nodule volume reduction was 68.87% ± 15.27 (range, 47.35%–94.89%). When the relative size of our treated nodules was taken into consideration, these results compared favorably to those of other studies (12–14). One underlying reason for this might have been that our HIFU machine was equipped with the latest ablation software (Beamotion; Theraclion), which permitted a greater amount of ultrasonic energy to be delivered to the targeted nodule, and thereby, allowed a greater ablation volume to be achieved in a shorter period of time. Despite delivery of a similar amount of HIFU energy per treatment, the mean treatment time in our study, which included both planning and ablation, was shorter (75.71 minutes ± 34.20 vs 86.8 minutes ± 31.7, respectively) and nodule reduction at 6 months appeared greater (66.91% ± 16.27 vs 48.7% ± 24.3, respectively) relative to those of a previous study (13).

Although no significant size change was seen in the first week, noticeable shrinkage was seen after 1 month. This was consistent with the fact that it normally takes weeks for an ablated area to be absorbed by the inflammatory cells (12). Although there was progressive size reduction at 3, 6, and 12 months, the reduction rate was greatest in the first 3 months. The implication of this is that, perhaps for patients with a less satisfactory response (ie, < 50% volume reduction) in the first 3 months, a reapplication of HIFU could be considered earlier instead of waiting longer for a satisfactory response. These findings are consistent with those observed with other thermal ablation techniques (18).

From our experience, HIFU ablation is a safe and well-tolerated procedure. There was no significant morbidity and all patients underwent ablation successfully. Although patients felt some pain during ablation, they found it tolerable, and it subsided quickly after ablation. Approximately one-fourth of our patients did have pain radiating to their shoulders and arms. Perhaps this might have been referred pain arising from the ipsilateral cervical plexus during HIFU energy transfer from the skin to the thyroid. Perhaps, in the future, unilateral cervical plexus blocks may alleviate this type of neuropathic pain.

Similar to results of previous studies (13,14), patient demographics, body habitus, estimated treated volume, total energy delivered, and treatment depth were not significantly associated with ablation success. Instead, smaller preablation volume was a significant predictor of ablation success. This finding is important, because there is currently no recommended nodule size threshold for HIFU ablation.

Perhaps one of the most important findings of our study was that,

Table 4

Changes in Domain and Summary Score Over Time

	Change from Baseline in Each Group					
	3-month Change		6-month Change		12-month Change	
Domain and Summary Score	Median	*P* Value	Median	*P* Value	Median	*P* Value
Physical functioning		.209		.196		.067
HIFU	0 (25.00)		0 (50.00)		0 (50.00)	
Control	0 (0.00)		0 (25.00)		0 (25.00)	
Role physical		.011*		.019*		.005*
HIFU	0 (6.25)		0 (12.50)		0 (25.00)	
Control	0 (0.00)		0 (0.00)		0 (12.50)	
Bodily pain		.067		.029*		.008*
HIFU	0 (25.00)		0 (25.00)		0 (25.00)	
Control	0 (0.00)		0 (0.00)		0 (0.00)	
General health		.003*		.006*		.007*
HIFU	35 (40.00)		35 (40.00)		35 (40.00)	
Control	0 (0.00)		0 (0.00)		0 (25.00)	
Vitality		.097		.091		.176
HIFU	0 (25.00)		0 (25.00)		0 (25.00)	
Control	0 (0.00)		0 (0.00)		0 (0.00)	
Social functioning		.962		.006*		.006*
HIFU	0 (0.00)		0 (25.00)		0 (25.00)	
Control	0 (0.00)		0 (50.00)		−25 (50.00)	
Role emotional		.142		.104		.045*
HIFU	0 (12.50)		0 (12.50)		0 (12.50)	
Control	0 (0.00)		0 (0.00)		0 (0.00)	
Mental health		.537		.158		.105
HIFU	0 (12.50)		0 (25.00)		0 (25.00)	
Control	0 (0.00)		0 (25.00)		0 (25.00)	
Physical composite score		.001*		.025*		.006*
HIFU	4 (9.26)		2 (13.69)		5 (14.53)	
Control	0 (1.55)		−1 (3.87)		−1 (5.00)	
Mental composite score		.457		.107		.209
HIFU	0 (6.18)		1 (10.50)		0 (10.16)	
Control	0 (0.34)		0 (11.53)		0 (13.57)	

* Indicates a significant difference.

relative to a comparable group of patients who did not choose HIFU, those who underwent HIFU ablation had significantly lower pressure symptom scores and improvement in HRQOL at 12 months. We believe that our results were consistent with those of another study (19) in which patients who had a symptomatic nodule or goiter tended to have impaired HRQOL compared with that of their age- and sex-matched peers who did not undergo HIFU. In our study, the HRQOL scores were impaired relative to the population norm (20), but the HRQOL in the HIFU group gradually normalized after treatment, while the same was not observed in the surveillance group. More than 60% of patients in the HIFU group claimed "significant" symptom improvement, whereas no patients in the surveillance group claimed "significant" improvement in the same period. We believe that this symptom improvement together with the physical nodule reduction might be responsible for the improvement in patients' HRQOL (or more specifically, the physical composite score). This finding was supported by the fact that the improvement in physical composite score significantly correlated with the 6-month reduction in nodule size ($P < .001$) and 12-month reduction in nodule size ($P < .001$).

To date, and to our knowledge, authors of only one previous study (19) have reviewed changes in HRQOL after treatment of a goiter, and the authors found no change in all eight domains of the short form-12 questionnaire 6 months after surgery. However, surgery is generally more invasive and may have resulted in morbidities. On the other hand, HIFU ablation is a safe, noninvasive treatment and therefore, we believe that the improvement in five of the eight domains at 12 months after HIFU was genuine.

Although some may find it difficult to understand how a relatively small thyroid nodule (with a mean volume of 6.98 mL ± 4.04 and longest diameter of 3.14 cm ± 0.75) would cause pressure symptoms and impair HRQOL, recent evidence (21) suggests that even a thyroid nodule as small as 1.5 cm may lead to local discomfort and symptoms. Therefore, it is plausible that a significant nodule shrinkage after HIFU ablation could have led to significant improvement in pressure symptoms and HRQOL.

However, despite these findings, we would like to acknowledge several shortcomings in our study, First, this was a nonrandomized study and selection biases could have influenced some of the more subjective results (such as symptom and HRQOL scores). It was possible that patients who underwent HIFU treatment anticipated a higher level of improvement than did those who did not undergo treatment. Nevertheless, our study results have provided sufficient support for a randomized study in the future. Second, our study was relatively small, and so our results were prone to type II errors.

In conclusion, patients who underwent a single session of HIFU ablation as treatment for a symptomatic benign thyroid nodule not only had significant (mean > 60%) nodule volume reduction on US images but also improved pressure symptom score and HRQOL throughout a 12-month period. As a result, US-guided HIFU ablation is a better therapeutic option than is active surveillance for patients who have a symptomatic benign thyroid nodule but do not wish to undergo surgical resection.

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